UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,000	06/09/2005	Pieter Jan Arnoldus Maria Plomp	4662-25	8720

23117 7590 10/25/2010

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
10/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

1. Claims 1-9, 22-26, 28-29, 32-40 are pending.

2. The request for entering amendments to claims 24, 34, 36, 39 and arguments filed on 9/28/2010 under 37 CFR 1.116 in reply to the Final Action mailed on 12/28/2009 are acknowledged. The proposed amendments to the claims will be entered. The amendments to the claims overcome the 35 USC 112, second paragraph and new matter rejections previously applied. However, the amendments to the claims do not place the instant application in condition for allowance for the reasons of record and those set forth below.

3. With regard to the rejection of claim 23 under 35 USC 112, first paragraph, written description, Applicant argues that the section "Functional equivalents" provides examples of how one could obtain functional equivalents of the polypeptide of SEQ ID NO: 3. Specifically, applicant states that the specification teaches how conservative substitutions can be made. Applicant also refers to the teachings of the art regarding phenotypically silent amino acid substitutions. Therefore, one could appreciate highly homologous polypeptides which still maintain asparaginase activity. According to applicant, Seffernick et al. negates the conclusion that protein engineering would be totally unpredictable because they teach that proteins having more than 98% sequence identity and having different enzymatic activity is exceptional. It is applicant's contention that a person of ordinary skill in the art is capable of mutating a gene in a predictable way, especially when staying within the 95% sequence identity frame.

4. Applicant's arguments have been fully considered but not deemed persuasive to overcome the instant rejection. The Examiner acknowledges that how to make conservative substitutions is known in the art. The examiner also acknowledges the teachings of Seffernick et al. However, the examiner disagrees with applicant's contention that determining a priori without any additional information as to how structure correlates with function which structural variants of the polypeptide of SEQ ID NO: 3 would have asparaginase activity would be accurately determined by one of skill in the art. The

teachings of Seffernick et al. were provided as an example to show that structural homology does not always correlate with functional homology. As previously indicated, the teachings of Loubody are further evidence that there structural/functional variability among asparaginases from *A. niger*. See discussion of the teachings of Loubody in the previous Office action. Even if the argument is made that the findings of Seffernick et al. are not common, these findings along with those of Witkowski et al. further support the teachings of Branden with regard to the unpredictability of accurately determining function based solely on structural homology. Neither the specification nor the art provide a structure/function correlation which would allow one of skill in the art to distinguish out of the essentially infinite number of structural variants of the polypeptide of SEQ ID NO: 3, which ones have asparaginase activity. See calculation of the number of variants which are the result of substitutions in the previous Office action. While one could make any number of conservative substitutions to a protein, one of skill in the art would not expect that any conservative substitutions would yield a variant with the same enzymatic activity. See the teachings of Witkowski et al. where it is shown that conservative substitutions resulted in a different enzymatic activity. Therefore, contrary to applicant's assertions, one cannot reasonably conclude that it is predictable to obtain a variant of the polypeptide of SEQ ID NO: 3 with asparaginase without any information as to how structure correlates with function. It is noted that applicant has referred to a 95% homology frame, however claim 34, which recites "95% identical" has not been rejected under this statute.

5. With regard to the rejection of claims 22-25, 32, 40 under 35 USC 112, first paragraph, scope of enablement, applicant argues that the specification teaches a person skilled in the art to make asparaginases according to the invention and confirm their enzymatic activity, and that the amount of experimentation required is not undue. The Examiner reiterates that the number of structural variants of the polypeptide of SEQ ID NO: 3 recited in the claims is essentially infinite. See extensive discussion and calculations provided in the prior Office action. Therefore, it is the Examiner's position that testing

an infinite number of variants to determine which ones have the desired activity without any teaching or guidance as to which are the structural features most likely to be associated with the desired activity so that the level of testing is limited to a reasonable amount would require undue experimentation. It is also noted that under the wash conditions recited, Tm according to the equation of Meinkoth and Wahl would be reduced to 78.61 C (0.2xSSC and 25 C). The % mismatching under these conditions is 53.61% (= 78.61 C- 25 C; at least 46.39% (100% - 53.61%) sequence identical to the polynucleotides of SEQ ID NO: 1 or 2). While the hybridization conditions result in approximately 33.8% mismatching (at least 66.2% sequence identical to the polynucleotides of SEQ ID NO: 1 or 2; see calculations in prior Office action), there is the potential for obtaining nucleic acids which have higher % mismatching if the wash conditions are less stringent than the hybridization conditions, which is the case herein.

6. With regard to the rejection of claims 24, 32 and 40 under 35 USC 102(b) as being anticipated by Minton et al., applicant argues that the *A. niger* asparaginase of Minton et al. does not anticipate the instant claims because the claims refer to the full length complement and that a polypeptide having 40% sequence identity would not hybridize to the full length complement of the polynucleotides of SEQ ID NO: 1 or 2.

7. Applicant's arguments have been fully considered but not deemed persuasive. Even if the argument is made that the claims recite "hybridizes…to the full length complement of the polynucleotide of SEQ ID NO: 1 or SEQ ID NO: 2" or that the hybridization reaction occurs between the full-length complement of the polynucleotide of SEQ ID NO: 1 or 2, it is reiterated herein that the asparaginase of Minton et al., which is 43.1% sequence identical to the polypeptide of SEQ ID NO: 3, can be encoded by a nucleic acid which is 66.2% sequence identical to the polynucleotide of SEQ ID NO: 1 or 2. As explained before, a nucleic acid which is 66.2% sequence identical to the polynucleotide of SEQ ID NO: 1 or 2 (% identity that is equivalent to the hybridization conditions recited in the claims) can potentially encode a protein having little structural homology to the polypeptide of SEQ ID NO: 3 since this level of

identity amounts to up to 384 mismatches in the polynucleotide of SEQ ID NO: 1 or 2. See prior Office action for calculations. If most of these mismatches affect a codon, one could have a situation where the protein encoded by the 66.2% nucleic acid variant would have very little sequence identity with the polypeptide of SEQ ID NO: 3, which is 378 amino acids long. For example, one could have a nucleic acid which is 66.2% sequence identical to the polynucleotide of SEQ ID NO: 1 or 2 having 384 mismatches with respect to the polynucleotides of SEQ ID NO: 1 or 2, wherein the 384 mismatches result in 215 codons affected. Then, that nucleic acid which is 66.2% sequence identical to the polynucleotide of SEQ ID NO: 1 or 2 would encode a protein having 43% sequence identity with the polypeptide of SEQ ID NO: 3 (43% = 100% - 215x100/378). Therefore, for the reasons of record and those set forth above, the asparaginase of Minton et al. anticipates the instant claims as written.

8. Claim 34 is now objected to as being dependent upon a rejected base claim.

9. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: 33, 34

Claim(s) rejected: 22-25, 32, 40

Claim(s) withdrawn from consideration: 1-9, 26, 28-29, 35-39

10. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from

either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Examiner
Art Unit 1652

DR
October 25, 2010